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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/695,667	10/27/2003	Paul J. Maddon	P0741.70006US00	4456

7590 02/16/2007

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/695,667	MADDON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-101 and 169-193* is/are pending in the application.

4a) Of the above claim(s) *169-186* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-101 and 187-193* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20040929;20051215*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The election without traverse filed November 29, 2006, is acknowledged and has been entered.

Applicant has elected the invention of Group I, claims 1-101 and 187-193, drawn to a composition comprising isolated PSMA protein, or a kit comprising said composition.

2. The amendment filed November 29, 2006, is acknowledged and has been entered. Claims 102-168 have been canceled. Claims 19, 74, and 170 have been amended.

3. Claims 1-101 and 169-193 are pending in the application. Claims 169-186 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 29, 2006.

4. Claims 1-101 and 187-193 are currently under prosecution.

Information Disclosure Statement

5. The information disclosures filed September 27, 2004, and December 13, 2005, have been considered. An initialed copy of each is enclosed.

Priority

6. Applicant's claim under 35 U.S.C. §§ 119 and/or 120 for benefit of the earlier filing date of Application No. 10/395,894, filed March 21, 2003, which claims benefit of U.S. Provisional Application No. 60/335,215, filed October 23, 2001, U.S. Provisional Application No. 60/362,747, filed March 7, 2002, and U.S. Provisional Application No. 60/412,618, filed September 20, 2002, is acknowledged.

However, claims 1-101 and 187-193 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely October 27, 2003.

Drawings

7. The drawing set forth as Figure 13 is objected to because the figure depicts nucleic acid and amino acid sequences, which are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 18 of the specification. Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the brief description of the figure at page 4 of the specification to include sequence identification numbers.

Specification

8. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figure 13 are not identified by sequence identification numbers, either in the figure or in the brief description of figure at page 18.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

9. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is BiaCore™ (see, e.g., page 29, line 23).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such an impermissible disclosure appearing in the specification is found in paragraph [0177] of the published application[1].

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

Claim Objections

11. Claim 20, 64, and 68 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 20 is drawn to the composition of claim 19, wherein the adjuvant is alum. Claim 19 is drawn to the composition of claim 18, wherein the adjuvant is selected from the list of adjuvants recited in the claim or a combination thereof. The adjuvant to which

[1] U.S. Patent Application Publication No. 2004/0161776 A1.

claim 19 is directed is therefore not necessarily alum, since, for example, the adjuvant to which claim 19 is directed is possibly monophosphoryl lipid A; and monophosphoryl lipid A is not alum. Accordingly, claim 20 does not properly limit claim 19 as it does not further limit each and every embodiment of the invention of claim 19.

It is suggested this issue be remedied by amending claim 20 to depend from claim 18, rather than from claim 19.

Claim 64 is drawn to the composition of claim 63, wherein the metal ions are zinc and calcium ions. Claim 63 is drawn to the composition of claim 62, wherein the metal ions are zinc ions, calcium ions, magnesium ions, cobalt ions, manganese ions or a combination thereof. The metal ions to which claim 63 is directed are therefore not necessarily zinc ions or calcium ions, since, for example, the metal ions to which claim 63 is directed are possibly manganese ions; and manganese ions are not zinc or calcium ions. Accordingly, claim 64 does not properly limit claim 63 as it does not further limit each and every embodiment of the invention of claim 63.

For essentially this same reason, claim 68, which is directed to the composition of claim 63, wherein the metal ions are magnesium ions, does not properly limit claim 63.

These issues may be remedied by amending claims 64 and 68 to depend from claim 62, as opposed to claim 63.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claim 193 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific and substantial asserted utility, a credible asserted utility, or a well-established utility.

The considerations that are made in determining whether a claimed invention is supported by either a specific and substantial asserted utility or a well-established utility

are outlined by the published Utility Examination Guidelines (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: http://www.gpoaccess.gov/.

Briefly, a "specific and substantial" asserted utility is an asserted utility that is specific to the particular nature and substance of the claimed subject matter, and which would be immediately available for application in a "real-world" context by virtue of the existing information disclosed in the specification and/or on the basis of knowledge imparted by the prior art, such that its use would not require or constitute carrying out further research to identify or reasonably confirm its usefulness in this context. A "well-established" utility is a credible, specific, and substantial utility, which is well known, immediately apparent, and implied by the specification, and based on the disclosure of the properties of a material or subject matter, either alone or taken with the knowledge of one skilled in the art.

Claim 193 is drawn to a pharmaceutical composition (i.e., a composition that is intended for use in a pharmacologic or medicinal application, such as therapy).

However, while the specification describes how such pharmaceutical compositions comprising a composition comprising isolated PSMA protein, wherein at least 5% of the isolated PSMA protein is an isolated PSMA protein multimer, are made or formulated, *the specification is silent as to how such the claimed invention is used.*

The only relevant disclosure in the specification is found in paragraph [0254] of the published application, which reads:

> Pharmaceutical compositions of the invention also can be administered in combination therapy, i.e., combined with other agents. For example, the combination therapy can include a composition of the present invention with at least one anti-tumor agent, immunomodulator, immunostimulatory agent, or other conventional therapy. The agent may be bound or conjugated to or formed as a recombinant fusion molecule with the PSMA antibodies of the present invention for directed targeting of the agent to PSMA-expressing cells.

This disclosure, however, does not provide an assertion as to *how* the claimed invention is used by the practitioner of the relevant art of pharmacology and/or medicine in a specific and substantial manner to achieve any particular therapeutic benefit to the patient or subject to whom it is administered for such purpose.

The utility requirement set forth under 35 U.S.C. § 101 has been addressed by the United States Supreme Court in *Brenner, Comr. Pats. v. Manson,* 148 U.S.P.Q. 689 (US SupCt, 1966). The court decided § 101 requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The Court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. Id., at 695.

The Court further opined:

> [W]e are [not] blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Id., at 696.

Utilities of inventions that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not "specific and substantial utilities". Because the specification does not describe *how* the invention is used, an immediate benefit could not be derived from using the claimed invention because it would first necessary to determine *how* the invention can be used. As such, any benefit that might be derived by the public for a grant of a patent monopoly of the existing information disclosed by Applicants' application could not be derived immediately and directly therefrom or without need to first complete the inventive process by performing additional experimentation to characterize the pharmacologic properties of the claimed composition. To fulfill the requirements of 35 USC § 101, the skilled artisan must be able to use a claimed invention in the manner asserted by Applicants' to provide some immediate benefit to the public. See *Nelson v. Bowler and Crossley*, 206 USPQ 881 (CCPA, 1980).

Notably, it cannot be presumed that the claimed invention has a specific and substantial utility, since it is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science.* 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of

sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Additionally, it is aptly noted that it cannot be presumed that the claimed invention can be used in a specific and substantial manner by the practitioner in conjunction or combination with any other established treatment modality to immediately benefit the patient or subject to whom the pharmaceutical composition is administered. This position is supported, for example, by the teachings of Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776). Saijo et al. recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Finally, because the claimed invention does not have an asserted specific and substantial utility, the credibility of its utility cannot be considered.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claim 193 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by a specific and substantial asserted utility, a credible asserted utility, or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As explained in the above rejection of claim 193 under 35 U.S.C. § 101, the specification describes the claimed pharmaceutical composition, but does not describe how the invention is used in a manner that might immediately benefit the public. As such, the claimed invention is not supported by a specific and substantial asserted utility.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or

absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Because the specification does not disclose how the invention is used, the amount of guidance, direction, and exemplification set forth in the specification would not reasonably enable the skilled artisan to make and use then use the claimed invention; and because the art is so highly unpredictable, it is unreasonable to presume that the claimed invention will have a specific and substantial utility.

Therefore, a patent granted upon this application's disclosure of the claimed subject matter should only be viewed as a mere invitation to the skilled artisan to elaborate a use for the claimed invention, or to finish the inventive process. The need to elaborate such a use, or to finish the inventive process would constitute a requirement that the practitioner perform undue and/or unreasonable experimentation before the claimed invention could be made and used in a manner that might ultimately benefit the public, or with a reasonable expectation of success.

16. Claims 1-101 and 187-193 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-101 and 187-193 are indefinite for the following reason: Claims 1-101 and 187-193 contain the term "PSMA", which is used as the sole means of identifying the polypeptide to which the claims refer. The use of such laboratory designations only to identify a particular polypeptide renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides, which are encoded by the same or different genes.

This issue may be remedied by amending the claims to include appropriate reference to the sequence identification number that identifies the amino acid sequence of the polypeptide to which the claims are directed, as set forth in the Sequence Listing of this application. Such an amendment would be remedial because the amino acid

sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide.

(b) Claim 3 is indefinite because of the parenthetical recitation of "SEQ ID NO: 1". It cannot be determined whether the parenthetical recitation is intended to limit the subject matter encompassed by the claim; or perhaps the amino acid sequence of SEQ ID NO: 1 is meant only to exemplify the amino acid sequence of "full-length PSMA" or the fragment thereof. If the parenthetical recitation is intended to limit the claimed subject matter, it is unclear whether the claim requires "full-length PSMA" or the fragment thereof to *comprise* the amino sequence of SEQ ID NO: 1, or perhaps instead to *consist of* this amino acid sequence. For these reasons, the claim fails to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

(c) Claim 4 is similarly indefinite because of the parenthetical recitation of "amino acids 44-750 of SEQ ID NO: 1". Here again it cannot be determined whether the parenthetical recitation is intended to limit the subject matter encompassed by the claim; or perhaps amino acids 44-750 of SEQ ID NO: 1 is meant only to exemplify the amino acid sequence of the "extracellular portion of PSMA" or the fragment thereof. If the parenthetical recitation is intended to limit the claimed subject matter, it is unclear whether the claim requires the "extracellular portion of PSMA" or the fragment thereof to *comprise* amino acids 44-750 of SEQ ID NO: 1, or perhaps instead to *consist of* this portion of the amino acid sequence. For these reasons, the claim fails to delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity.

(d) Claim 19 is indefinite for the following reason: Claim 19 contains the trademark/trade names "ENHANZYN™" and Montanide™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope

is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the adjuvants to which the claim is directed and, accordingly, the identification/description is indefinite.

(e) Claim 19 is indefinite because the claim recites "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 18, which is directed to a composition of claim 1 further comprising *an* adjuvant. According to claim 19, *the* adjuvant is any one of the adjuvants selected from those adjuvants specifically recited in the claim. While each of the recited adjuvants is recognized as such, the combinations thereof are not. For example, alum and monophosphoryl lipid A are well known adjuvants; but an adjuvant that is a *combination* of alum and monophosphoryl lipid A is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different adjuvants to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

It is suggested that this issue be remedied by amending claim 18 to recite the limitation, "wherein the composition comprises at least one adjuvant", and then amending claim 19 to strike the recitation of "a combination thereof".

(f) Similarly claim 25 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 24, which is directed to a composition of claim 1 further comprising at least *one* buffer. According to claim 25, *the* at least one buffer is any one of the buffers selected from those buffers specifically recited in the claim. While each of the recited "buffers" is buffered solution (i.e., PBS) or otherwise a weak acid or a weak base recognized as having the capability of buffering the pH of a solution in which it is contained, the combinations thereof are not. For example, citric acid and

acetic acid are weak acids routinely used to pH buffer solutions; but a "buffer" that is a *combination* of citric acid and acetic acid is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different "buffers" to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

It is suggested that this issue be remedied by amending claim 19 to strike the recitation of "a combination thereof".

(g) Claim 28 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 27, which is directed to a composition of claim 26/1 further comprising a free non-acidic amino acid. According to claim 28, *the* free non-acidic amino acid is any one of the amino acids selected from those amino acids specifically recited in the claim. While each of the recited amino acids is recognized as such, the combinations thereof are not. For example, glycine and proline are amino acids; but the "amino acid" that is a *combination* of glycine and proline is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different amino acids to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

(h) Claims 30 and 78 are indefinite for the following reason: Claims 30 and 78 contains the trademark/trade name Tween™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or

describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the surfactant to which the claim is directed and, accordingly, the identification/description is indefinite.

(i) Claim 30 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 29, which is directed to a composition of claim 1 further comprising a surfactant. According to claim 30, *the* surfactant is any one of the surfactants selected from those surfactants specifically recited in the claim. While each of the recited surfactants is recognized as such, the combinations thereof are not. For example, Tween™-20 and Triton X-100 are used as surfactants; but the "surfactant" that is a *combination* of Tween™-20 and Triton X-100 is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different surfactants to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

(j) Claims 43-47 are indefinite because the claims recite limitations that the composition of claim 43 comprises less than 35% of a monomeric PSMA protein, but do not indicate how the percentage is calculated. Is the percentage determined using a fraction calculated as the value of a weight per weight, a weight per volume, or a volume per volume? Relative to what other component of the composition is the percentage of monomeric PSMA in the composition determined? Is the percentage calculated as an expression of the fraction of monomeric PSMA protein to total PSMA, or perhaps as an expression of the fraction of monomeric PSMA protein to multimeric PSMA? The metes and bounds of the subject matter that is regarded as the invention are not delineated with the requisite clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, and to thereby permit the skilled artisan to know or determine infringing subject matter.

(k) Claims 50-53 are indefinite because claim 50 recites the limitation, "the solution that promotes or preserves dimeric association of PSMA protein". There is no

antecedent basis in preceding claim 48 to support the recitation of this limitation in claim 50 because the solution of claim 48 promotes or preserves *multimeric* association of PSMA protein, but not necessarily dimeric association of the protein.

(l) Claims 54-61 are indefinite because claim 54 recites the limitation, "the solution that promotes or preserves dimeric association of PSMA protein". There is no antecedent basis in preceding claim 48 to support the recitation of this limitation in claim 54.

(m) Claims 55-61 are indefinite because of the recitation by claim 55 of "a combination thereof". This recitation renders the claims indefinite because claim 55 is drawn to the composition of claim 54, which is directed to a composition of claim 48, wherein the solution that promotes or preserves dimeric association of PSMA protein comprises a salt. According to claim 55, *the* cationic and anionic components of the salt are any one of the cationic and anionic components selected from those specifically recited in the claim. While each of the recited cationic and anionic components is recognized as such, the combinations thereof are not. For example, sodium and potassium are metals, which could be the cationic components of certain salts; but the "cationic component of the salt" that is a *combination* of sodium and potassium is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different cationic and anionic components to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

(n) Claims 55-61 are indefinite because claim 55 recites the limitations, "the cationic component of the salt" and "the anionic component of the salt". There is insufficient antecedent basis in the preceding claims 54/48 to support the recitation of these limitations in claim 55 because the "solution" is not necessarily an aqueous solution in which the salt is soluble; only upon dissolution in an aqueous solution is a salt generally capable of forming cations and anions.

(o) Claims 62-70 are indefinite because claim 62 recites the limitation, "the solution that promotes or preserves dimeric association of PSMA protein". There is no antecedent basis in preceding claim 48 to support the recitation of this limitation in claim 62.

(p) Claim 71 is indefinite the claim recites the limitation, "the solution that promotes or preserves dimeric association of PSMA protein". There is no antecedent basis in preceding claim 48 to support the recitation of this limitation in claim 71.

(q) Claim 73 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 72, which is directed to a composition of claim 48 further comprising at least *one* buffer. According to claim 73, *the* at least one buffer is any one of the buffers selected from those buffers specifically recited in the claim. While each of the recited "buffers" is buffered solution (i.e., PBS) or otherwise a weak acid or a weak base recognized as having the capability of buffering the pH of a solution in which it is contained, the combinations thereof are not. For example, citric acid and acetic acid are weak acids routinely used to pH buffer solutions; but a "buffer" that is a *combination* of citric acid and acetic acid is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different "buffers" to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

(r) Claim 76 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 75, which is directed to a composition of claim 74/48 further comprising a free non-acidic amino acid. According to claim 76, *the* free non-acidic amino acid is any one of the amino acids selected from those amino acids specifically recited in the claim. While each of the recited amino acids is recognized as such, the combinations thereof are not. For example, glycine and proline are amino acids; but the "amino acid" that is a *combination* of glycine and proline is not well

known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different amino acids to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

(s) Claim 78 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 77, which is directed to a composition of claim 48 further comprising a surfactant. According to claim 78, *the* surfactant is any one of the surfactants selected from those surfactants specifically recited in the claim. While each of the recited surfactants is recognized as such, the combinations thereof are not. For example, Tween™-20 and Triton X-100 are used as surfactants; but the "surfactant" that is a *combination* of Tween™-20 and Triton X-100 is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different surfactants to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention; and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

(t) Claim 101 is indefinite because of the recitation by the claim of "a combination thereof". This recitation renders the claim indefinite because claim is drawn to the composition of claim 95, which comprises at least one metal ion. According to claim 101, *the* metal ion is any one of the metal ions selected from those surfactants specifically recited in the claim. While each of the recited metal ions is recognized as such, the combinations thereof are not. For example, zinc ions and calcium ions are recognized as metal ions; but the "metal ion" that is a *combination* of a zinc ion and a calcium ion is not well known, and its structure has not been described in the specification. Absent any description in the specification of the combinations of these various different metal ions to which the claim is directed, it is submitted the claim is directed to subject matter that is not actually regarded by Applicant as the invention;

and therefore, the claim fails to clearly delineate the subject matter that Applicant regards as the invention.

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1-101 and 187-193 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or

> relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention.*

In this instance, the claims 1-101 and 187-193 are directed to a genus of "PSMA proteins" that are capable of forming multimeric complexes comprising of a plurality of one or more species of "PSMA protein".

The specification discloses at paragraph [0013] of the published application the following:

> In some embodiments the PSMA protein multimers comprise the full-length PSMA protein (SEQ ID NO: 1) or a fragment thereof. In other embodiments the PSMA protein multimer comprises the extracellular portion of PSMA (amino acids 44-750 of SEQ ID NO: 1) or a fragment thereof. In still other embodiments the PSMA protein multimer comprises the amino acids 58-750 of SEQ ID NO: 1 or a fragment thereof. In yet other embodiments the PSMA protein multimer comprises the amino acids 610-750 of SEQ ID NO: 1 or a fragment thereof. The fragments are capable of forming a PSMA multimer that can be used to generate antibodies that recognize PSMA, preferably native PSMA dimer. Typically, the PSMA multimers are homomultimers, meaning that the two or more PSMA molecules are the same. In other embodiments, the PSMA multimers are

> heteromultimers, whereby at least two of the PSMA proteins are not the same. In still other embodiments the PSMA proteins can be functionally equivalent proteins, whereby the PSMA protein is conservatively substituted.

Then, at paragraph [0160] of the published application, the specification defines the term "PSMA protein" as inclusive of the full-length PSMA protein (provided as SEQ ID NO: 1) or a portion thereof; and at paragraph [0162] the specification describes the PMSA protein, which is capable of forming multimers, particularly dimers, as inclusive of the full-length protein (SEQ ID NO: 1), the extracellular portion of PSMA (amino acids 44-750 of SEQ ID NO: 1), or an alternatively spliced form of PSMA.

Given these disclosures it is apparent that members of the genus of "PSMA proteins" to which the claims are directed may vary substantially in structure and/or function; however, the genus has not be described in a manner that would permit the skilled artisan to immediately envision, recognize or distinguish its members from others because the members of the genus do not necessarily share any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also common among its members.

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant

was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.
[0169] An "agent that preserves or promotes the dimeric association of PSMA" is meant to encompass an agent that promotes or maintains the dimerization of PSMA. Such agents have been found to include pH adjusting agents (as discussed above), metal ions and salts. It has been discovered that these agents, individually or in combination, are able to preserve or promote dimeric association of PSMA.

Furthermore, claims 48-101 are directed to a genus of "solutions", which promote or preserve multimeric association of PSMA protein, but which vary substantially in composition comprising any of several different salts at any of widely varying concentrations, any of several different metals ions at any of widely varying concentrations, any of several different buffers, free amino acids, surfactants, cryoprotectants, antioxidants, and preservatives, and having a varying pH.

In contrast to the evident breadth of the claims, the specification merely discloses at paragraph [0171] of the published application, for example, that it has been found that salts preserve or promote PSMA dimerization, and as shown in the examples, a dimer preparation that contained approximately 5% monomer initially was converted to 100% dimer upon incubation for 72 hours at ambient temperature in PBS+ (phosphate-buffered saline containing 1 mM Ca^{2+} and 0.5 mM Mg^{2+}, pH 7.2) supplemented with 2M sodium chloride.

Given the significant difference between the breadth of the claims and the scope of the supporting disclosure, it is submitted that the specification would merely present an invitation to the skilled artisan to experimentally determine the effects of varying one or more of the components or properties of the exemplary composition upon the multimerization of "PSMA proteins", which if found to comparably promote or preserve

the association of the proteins would then fall within the scope of the subject matter that Applicant now seeks to patent.

However, not having described the effects that such wide variation of the composition and properties of the solution of which the claimed invention is comprised, which promotes and preserves multimeric association of "PSMA proteins" in such a complete and detailed manner to permit the skilled artisan to predict by extrapolation of such disclosures the effects of more widely varying its composition and properties, albeit within the confines of the claims, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

To the contrary, it is submitted that the specification provides an indication that the effects of such variations of the composition and properties of the solution of which the claimed composition is comprised are largely unpredictable, and must instead be determined empirically. For example, at paragraph [0177] of the published application, the specification discloses the effect of free amino acids on the dimeric state of rsPSMA (2 mg/ml in PBS+) dialyzed into 20 mM sodium acetate and 150 mM NaCl at a pH of about 6 was also tested, and in general it was found that free amino acids did not have a strong negative effect on dimer association of PSMA and/or column recovery, *with the exception of histidine, glutamic acid and aspartic acid* used individually at the specific experimental conditions.

Notably, given the finding that certain free amino acids negatively impacted the association of "PSMA proteins", the specification discloses the formulations can also include a free amino acid or combination of free amino acids, *provided that the free amino acid does not have a negative effect that outweighs the dimeric association promoting or preserving nature of the specific formulation.* However, it is not sufficient to so generally describe the subject matter that Applicant regards as the invention, if the written description requirement is to be satisfied.

"[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes the genus of solutions that promote or preserve multimeric association of "PSMA proteins". A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability of a substance to promote or preserve dimeric association of PSMA proteins, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding the solutions the

ability of a substance to promote or preserve dimeric association of PSMA proteins, which can be used to make the claimed invention; without such solutions, it is impossible to practice the invention.

Although the skilled artisan could potentially identify solutions that might be used in making the claimed invention by empirically determining the effects of various alterations in the composition or properties of the exemplary solution upon the association of PSMA proteins, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Finally, claims 91-94 are directed to the composition of claim 48, which is *stable* when stored at varying temperatures ranging from -80 °C (claim 91) to room temperature (claim 94).

While the term "stable" does not appear to be explicitly defined in the specification, the term is defined by Stedman's Online Medical Dictionary, 27th Edition (available on the Internet at http://www.stedmans.com) as meaning: "not varying; resistant to change" (Copyright © 2007 Lippincott Williams and Wilkins).

Given the fact that material nature of the claimed composition itself (i.e., the composition of claim 48) does not vary, it follows that what may not be "stable" at a relatively low temperature (e.g., 4 °C) will be substantially less "stable" at higher temperatures (e.g., room temperature, or typically about 20 °C).

For this reason, it would appear that the specification has not adequately described the claimed invention with the requisite degree of particularity to satisfy the written description requirement because, for example, the specification does not distinguish a composition according to claim 48, which is "stable" at any one of the specifically recited temperatures (-80 °C, -20 °C, 4 °C, and room temperature) from a composition according to claim 48, which is "stable" at any other of these temperatures, and the skilled artisan cannot predict which compositions are "stable" at which temperatures, as the stability of such compositions can only be determined empirically.

19. Claims 1-101 and 187-192 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a composition comprising the polypeptide of SEQ ID NO: 1 or a fragment thereof and a kit comprising said composition, **does not reasonably provide enablement for making and using** the claimed subject matter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the

art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As discussed in the above rejection of the claims, as failing to comply with the written description requirement, the claims are directed to a genus of structurally and/or functionally disparate proteins, which includes but is not limited to the polypeptide of SEQ ID NO: 1 and fragments thereof. For example, according to the disclosure at paragraph [0013] of the published application, "the PSMA proteins can be functionally equivalent proteins", so the proteins are not necessarily structurally related to the polypeptide of SEQ ID NO: 1, but may have some equivalent function (e.g., carboxypeptidase activity).

In contrast to the breadth of the claims, however, the specification teaches isolation of the native polypeptide of SEQ ID NO: 1, as well as the production and purification of a recombinant, soluble polypeptide that is an extracellular portion of the native polypeptide, which consists of the amino acid sequence spanning the residues at positions 44 and 750 of SEQ ID NO: 1; see, e.g., Example 15 at paragraphs [0384]-[0403] of the published application.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be

provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a "PSMA protein" that is functionally equivalent to the polypeptide of SEQ ID NO: 1, for example, for use in making and using the claimed invention; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

Additionally, as also discussed in the above rejection of the claims, as failing to comply with the written description requirement, the claims are directed to a genus of "solutions" that are capable of promoting or preserving multimeric association of "PSMA proteins", which can be used to make the claimed invention.

In this regard, the specification discloses the recombinant, soluble polypeptide ("rsPSMA") is capable of forming homodimers; see, e.g., paragraph [0388] of the published application.

Furthermore, the specification describes a study of monomer-dimer equillibria using "rsPSMA" in Example 33 at paragraphs [0480] and [0481] of the published application, which disclose the following:

> [0480] Purified dimeric and monomeric forms of rsPSMA were resolved by preparative size exclusion chromatography (SEC) in PBS+ buffer and collected in separate fractions. To assess whether dimer and monomer exist in a reversible equilibrium, the buffer conditions were perturbed, and the monomer-dimer ratio was analyzed by SEC. As indicated in FIG. 53A, a dimer preparation that contained approximately 5% monomer initially was converted to 100% dimer upon incubation for 72 h at ambient temperature in PBS+ supplemented with 2M sodium chloride (FIG. 53A). Conversely, the addition of 2 mM of the metal-chelating agent EDTA converted the dimer into monomer with a half-life of approximately 2 days (FIG. 53A), indicating that dimer stability is dependent upon the presence of metal ions, such as Zn^{2+} in the active site of PSMA.
>
> [0481] For a preparation that initially comprised >95% monomer, high salt similarly drove the equilibrium to mostly (81%) dimer within 72 h (FIG. 53B). EDTA had little influence on the oligomeric state of the monomer. Thus, regardless of the initial oligomeric state of the protein, high salt concentrations promoted dimerization, whereas metal-chelating agents dissociated dimers into monomers.

These disclosures, however, would not reasonably enable the skilled artisan to make the claimed invention using the widely varying solutions to which the claims are directed, which comprise any of several different salts at any of substantially differing concentrations, any of several different metals ions at any of substantially differing concentrations, any of several different buffers, free amino acids, surfactants, cryoprotectants, antioxidants, and preservatives, and having substantially differing pH.

Again, in contrast to the evident breadth of the claims, the specification merely discloses at paragraph [0171] of the published application, for example, that it has been found that salts preserve or promote PSMA dimerization, and as shown in the examples, a dimer preparation that contained approximately 5% monomer initially was converted to 100% dimer upon incubation for 72 hours at ambient temperature in PBS+ (phosphate-buffered saline containing 1 mM Ca^{2+} and 0.5 mM Mg^{2+}, pH 7.2) supplemented with 2M sodium chloride.

Given the significant difference between the breadth of the claims and the scope of the supporting disclosure, it is submitted that the specification would merely present an invitation to the skilled artisan to experimentally determine the effects of varying one or more of the components or properties of the exemplary composition upon the multimerization of "PSMA proteins", which if found to comparably promote or preserve the association of the proteins would then fall within the scope of the subject matter that Applicant now seeks to patent.

Furthermore, it is submitted that the specification provides an indication that the effects of such variations of the composition and properties of the solution of which the claimed composition is comprised are largely unpredictable, and must instead be determined empirically. For example, at paragraph [0177] of the published application, the specification discloses the effect of free amino acids on the dimeric state of rsPSMA (2 mg/ml in PBS+) dialyzed into 20 mM sodium acetate and 150 mM NaCl at a pH of about 6 was also tested, and in general it was found that free amino acids did not have a strong negative effect on dimer association of PSMA and/or column recovery, *with the exception of histidine, glutamic acid and aspartic acid* used individually at the specific experimental conditions.

Accordingly, not having described the effects that such wide variation of the composition and properties of the solution of which the claimed invention is comprised, which promotes and preserves multimeric association of "PSMA proteins" in such a complete and detailed manner to permit the skilled artisan to predict by extrapolation of such disclosures the effects of more widely varying its composition and properties, albeit within the confines of the claims, the specification would not reasonably enable the skilled artisan to make the claimed invention without undue and/or unreasonable experimentation.

Finally, whereas claim 1, for example, is directed to a composition comprising "PSMA proteins", which are at least 5% multimeric, or at most 95% monomeric, at paragraph [0012] of the published application, the specification discloses other embodiments at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of the isolated PSMA protein in the composition is in the form of a multimer. However, as noted above, the specification merely teaches, for example, a preparation that initially comprised >95% monomer, but which in the presence of high salt was driven over time toward an equilibrium at which 81% of the protein was dimeric; the specification does not teach the preparation of the claimed compositions in which only at least 25% of the protein is preserved in the form of a dimer (claim 8) or in which only at least 50 or 75% of the protein is dimeric (claims 9 and 10). Rather, as the specification teaches, certain conditions (e.g., high salt concentrations) drive the system toward an equilibrium at which substantially more protein is dimeric (i.e., 81% of the protein), without teaching how the composition and properties of the solution are "tweaked" to arrest the system at a disequilibria at which less protein is in the form of a dimer, so as to enable the skilled artisan to make the claimed compositions.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to have enabled the skilled artisan to make, and then use,

the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 1-12, 17, 23, 24, 26, 29-50, 54, 61-63, 71, 72, 74, 77-90, and 193 are rejected under 35 U.S.C. 102(b) as being anticipated by Carter et al. (*Proc. Natl. Acad. Sci. USA.* 1996 Jan; **93**: 749-753), as evidenced by Slusher et al. (*J. Biol. Chem.* 1990 Dec 5; **265** (34): 21297-21301), Robinson et al. (*J. Biol. Chem.* 1987 Oct 25; **262** (30): 14498-14506), and Schulke et al. (*Proc. Natl. Acad. Sci. USA.* 2003 Oct 28; **100** (22): 12590-12595) (of record; cited by Applicant).

The claims are drawn to a composition comprising an isolated PSMA protein, which comprises a fragment of the amino acid sequence of SEQ ID NO: 1, at least a portion of which associates with other molecules of the protein to form a multimer (e.g., a dimer).

At paragraph [0013], for example, of the published application, the specification defines the term "PSMA protein multimer" to include a complex of at least two PSMA proteins or fragments thereof, such as the full-length protein.

Full-length PSMA (e.g., the polypeptide of SEQ ID NO: 1) comprises fragments thereof. For example, the polypeptide of SEQ ID NO: 1 comprises a fragment of the extracellular portion of the polypeptide, such as amino acids 44-750 of SEQ ID NO: 1, amino acids 58-750 of SEQ ID NO: 1 and amino acids 601-750 of SEQ ID NO: 1.

At paragraph [0313], for example, of the published application, the specification defines the term "isolated" as meaning separated from its native environment and present in sufficient quantity to permit its identification or use.

Carter et al. teaches a composition of isolated PSMA protein that has enzymatic activity with the substrate and pharmacologic properties of the *N*-acetylated α-linked acidic dipeptidase (NAALADase); see, entire document (e.g., the abstract; page 751, Table 1).

Carter et al. teaches the enzymatic assay was performed by first solubilizing cells expressing PSMA protein in a solution containing 50 mM Tris-HCl buffer (pH 7.4 at 37 °C) and 0.5% Triton X-100. Carter et al. discloses that a volume of the lysates containing 20-100 mg of protein was assayed for NAAG-hydrolyzing activity according to the protocol described by Slusher et al (page 750, column 1); and according to Slusher et al. the assay used is described by Robinson et al., except for the inclusion in the assay of 1 mM $CoCl_2$ (page 21301, column 1).

According to Robinson et al., the assay was performed in a solution comprising 50 mM Tris-HCl buffer (pH 7.4) and a dipeptide substrate that is cleaved by the protein to form a free amino acid (page 14499, column 2). Furthermore, according to Robinson et al., the assay is free of chelating agents.

As evidenced by Schulke et al., PSMA occurs as a non-covalent homodimer of PSMA proteins in a native conformation under non-denaturing conditions and that dimerization is required for enzymatic activity; see entire document (e.g., the abstract).

Therefore, as evidenced by Schulke et al., Carter et al. teaches a composition comprising an isolated PSMA protein, at least a portion of which formed dimers, because otherwise the preparation of isolated PSMA protein would have lacked enzymatic activity.

Carter et al. does not teach the percentage of the molecules of PSMA that are present in the form of a dimer, nor does Carter et al. teach the specific activity of the preparation of isolated PSMA protein, so it cannot be determined what percentage of the total amount of PSMA protein in the preparation was present in the form of a dimer, but it is presumed that the amount of the dimer that is present in any given solution of PSMA protein is a function of the composition and properties of the solution.

Nevertheless, because the isolated PSMA of which the disclosed composition was comprised necessarily formed a dimer having enzymatic activity, absent a showing

of any difference, the product of the prior art and the claimed product are deemed the same.

Additionally, although the prior art does not teach the composition is stable at decreased temperatures, including room temperature, 4 °C, -20 °C, and -80 °C, because the composition comprised enzymatically active PSMA protein dimers at physiologic temperature (i.e., 37 °C), it is expected that dimers would not dissociate upon lowering the temperature of the preparation but that the enzymatic activity of the preparation would change dramatically.

The Office lacks the facilities and resources to establish that the product of the prior art does not possess the same material, structural, and functional characteristics as the claimed composition. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed composition is different than that taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977) and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Note: For clarity with regard to claims 13-16, which is not a rejected claim, because Carter et al. does not teach the specific activity of the preparation of isolated PSMA protein, the number of moles of the protein present in the volume of the preparation used in the assay cannot be determined; as such, although the assay of Carter et al. contained 1 mM metal ion (Co^{2+}), it is believed that the number of molar equivalents of the metal ion, relative to the number of moles of PSMA protein, cannot be determined.

Additionally, with respect to claims 91-94, although the prior art does not teach the composition is unstable at decreased temperatures, including room temperature, 4 °C, -20 °C, and -80 °C, the composition comprised enzymatically active PSMA protein dimers at physiologic temperature (i.e., 37 °C), and it is expected that while perhaps the dimers might not dissociate upon lowering the temperature of the preparation, the enzymatic activity of the preparation would change dramatically. Accordingly, given the above-mentioned definition of the term "stable", it is unlikely that the preparation disclosed by the prior art would be stable (i.e., not varying; or resistant to change) at

lower temperatures because the enzymatic activity of the preparation would progressively diminish upon its storage at decreasing temperatures.

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1-12, 17, 18, 21, 43-47, and 193 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 342-358, 360-362, and 364-370 of copending Application No. 10/395,894. Although the

conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 1-13, 17-26, 29, 31-52, 54-58, 60-66, 68, 69, 71-74, 77, 79-90, 95-97, 99-101, 187-193 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 13, 17-19, 22, 25, 27, 28, 30, 33, 35, 47, 48, 52-54, 58, 64, 66-68, 70, 75, 76, 100, 101, 104, 105, 107, 111, 112, 116, 117, 207, 208, 211, and 214 of copending Application No. 10/976,352. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The claimed inventions are so substantially similar that for the most part, the claimed subject matter of the copending application anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

25. Claims 1-13, 17-26, 29, 31-52, 54-58, 60-66, 68, 69, 71-74, 77, 79-90, 95-97, 99-101, 187-193 are directed to an invention not patentably distinct from claims 1, 2, 13, 17-19, 22, 25, 27, 28, 30, 33, 35, 47, 48, 52-54, 58, 64, 66-68, 70, 75, 76, 100, 101, 104, 105, 107, 111, 112, 116, 117, 207, 208, 211, and 214 of commonly assigned copending Application No. 10/976,352. Specifically, although the conflicting claims are

not identical, they are not patentably distinct from each other for the reasons set forth in the above rejection of the claims on the ground of nonstatutory obviousness-type double patenting.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned copending Application No. 10/976,352, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 35 U.S.C. 103(c) and 37 CFR 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

26. No claim is allowed.

27. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Troyer et al. (*Int. J. Cancer* 1995; **62**: 552-558) (of record; cited by Applicant) teaches a composition comprising an isolated PSMA protein multimer; see entire document (e.g., the abstract). Pinto et al. (*Clin. Cancer Res.* 1996 Sep; **2**: 1445-1451) teaches an enzymatically active preparation of PSMA comprising buffers and surfactant. Rojas et al. (*Analytical Biochem.* 2002; **310**: 50-54) teaches an enzymatically active preparation of GCPII (PSMA) comprising a buffer and metal ions. Ghosh et al. (*Prostate*. 2003 Oct 1; **57** (2): 140-151) teaches an enzymatically active

preparation of GCPII (PSMA); furthermore, Ghosh et al. teaches carbohydrate moieties linked to amino acids at specific sites within the extracellular domain of GCPII (PSMA) is necessary for enzymatic activity. Bacich et al. (*Mammalian Genome.* 2001; **12**: 117-123) teaches enzymatically active preparations of PSMA. Tiffany et al. (*Prostate.* 1999; **39**: 28-35) teaches enzymatically active preparations of PSMA. Su et al. (*Cancer Res.* 1995 Apr 1; **55**: 1441-1443) teaches alternatively spliced variants encoded by *PSMA*. Slusher et al. (*Prostate.* 2000; **44**: 55-60) teaches enzymatically active preparations of PSMA. Luthi-Carter et al. (*J. Pharm. Exp. Ther.* 1998; **286** (2): 1020-1025) teaches enzymatically active preparations of NAALADase (PSMA). Lapidus et al. (*Prostate.* 2000; **45**: 350-354) teaches enzymatically active preparations of PSMA.

Other art made of record but not relied upon is considered pertinent to Applicant's disclosure. Davis et al. (*Proc. Natl. Acad. Sci. USA.* 205 Apr 26; **102** (17): 5981-5986) teaches the crystal structure of PSMA. Barinka et al. (*Protein Sci.* 2004; **13**: 1627-1635) teaches glycosylation at specific sites within the extracellular domain of GCPII (PSMA) is necessary for enzymatic activity. Schmittgen et al. (*Int. J. Cancer.* 2003 Nov 1; **107** (2): 323-329) teaches alternatively spliced variants encoded by *PSMA*. Aggarwal et al. (*Prostate*. 2006 Jun 15; **66** (9): 903-910) compares the enzymatic activity of mouse, dog, monkey and human PSMA. Williams et al. (*Oligonucleotides.* 2006 Summer; **16** (2): 186-195) compares the enzymatic activity of PSMA isoforms.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stephen L. Rawlings, Ph.D.
Primary Examiner
Art Unit 1643

slr
February 13, 2007

Notice to Comply	Application No.	Applicant(s)	
	10/695,667	MADDON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency, Applicant must provide substitute copies of the Sequence Listing, together with an amendment directing its entry and a statement that both copies are the same and include no new matter, as further explained below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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